

RAISBECK, LARA, RODRÍGUEZ & RUEDA
MIEMBROS DE LA FIRMA
BAKER & MCKENZIE

AVENIDA 82 No. 10-62, Piso 6
TELÉFONO: (57-1) 634-1500
BOGOTÁ, D.C. COLOMBIA
WWW.BAKER.COM
OFFICE.BOGOTA@BAKERNET.COM

507

SEÑORES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03049777 00000002 Folios: 3
Fecha (AND): 2003-01-29 17:15:07
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref.: Expediente No. **00.049.777**

Solicitud de Patente de Invención Titulada:

“COMPUESTOS DE INDAZOL Y COMPOSICIONES
FARMACÉUTICAS PARA LA INHIBICIÓN DE
PROTEÍNA KINASA, Y MÉTODOS PARA SU USO”

Solicitante: **AGOURON PHARMACEUTICALS, INC.**

**SOLICITUD DE EXAMEN DE FONDO SEGÚN EL ARTICULO 44 DE LA
DECISION 486, GACETA No. 519**

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina de Naciones, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Adjunto recibo por el monto de \$ 335.000 pesos para cubrir la tasa correspondiente, según la Resolución 41687 del año 2002.

Atentamente,



CARLOS R. OLARTE
CC. No. 79'782.747 de Bogotá
T.P. 74.295

Anexos: Recibo por \$ 335.000 pesos

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 63,095
FECHA : SEPTIEMBRE 23 DE 2002

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00049777 00000002 Folios: 3
Fecha (AMD): 2003-01-29 17:15:07
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
JULIAN ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	050-00110-6	3135146	23/09/2002	38,825,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 00005-01-01 SOLICITUDES	05 EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
	TOTAL :	318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia



Industria y Comercio

SUPERINTENDENCIA

RECIBO OFICIAL DE CAJA : 3 - 1.042
FECHA : ENERO 10 DE 2003

SUPERINDUSTRIA Y COMERCIO

Radicacion : 80049777 00000002 Folios: 3

Fecha (AMD): 2003-01-29 17:15:07

Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION

DEPENDENCIA: 2028 DIVISION DE NUEVAS CREACIONES

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	VAL. PAGO	FECHA PAGO	VAL. PAGO
JULIAN ANDRES VARGAS	CONSIGNACION	BANCO BOGOTANO	050-00110 6	2000000	10-01-2003	15 879.100.00

***** D E M O N S T R A T I V O *****

CAUS. REQUISITOS	CONCEPTO	TOTAL CONCEPTO
1 50005-01-00 OTROS SERVICIOS DE PROPIEDAD	PRE VALOR COMPLEMENTO TARIFA ADE ANTO	17.000.00
	TOTAL	17.000.00

SON: DIEZ Y SIETE MIL PESOS

RECEPCIONABLE : _____

PERIODO DE DATA APLICADO AL EXPEDIENTE N. _____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

590
375
2006-06-15

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020

Bogotá, DC, 31 de mayo de 2006

Apoderado: Carlos Reinaldo Olarte

Oficio:

6509

ASUNTO

Radicación: 00-49777

Trámite 002

Evento 001

Actuación 430

Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

- ◆Capítulo descriptivo, folios 4 a 436;
- ◆Capítulo reivindicatorio, folios 437 a 446;
- ◆1° examen de forma, folios 453 y 454;
- ◆Respuesta técnica al 1° examen de forma, folios 456 y 457;
- ◆Solicitud de la cual se reivindica prioridad, junto con su traducción, folios 462 a 566;
- ◆2° examen de forma, folio 584;
- ◆Solicitud del examen de patentabilidad 597 a 589.

Objeto de la invención:

El título de la invención es "COMPUESTOS DE INDAZOL Y COMPOSICIONES FARMACEUTICAS PARA LA INHIBICIÓN DE PROTEÍNA KINASA, Y MÉTODOS PARA SU USO"

El objeto de la presente solicitud se refiere al compuesto derivados 3,6 di-sustituidos 1-H-indazol, proceso de obtención y composiciones que los contienen; estos compuestos se les ha observado su utilidad como inhibidores de la proteína kinasa.

Claridad de la solicitud:

En el artículo 30 de la decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

-En las reivindicaciones 1 a 10, no son claras y su alcance es ilimitado; las reivindicaciones son excesivamente amplias y especulativas, compuesto que se basan en un modelismo molecular que cubre cualquier 3,6-disustituido-1H-idazol, porque dicho modelismo o la formula Markush comprende una porción fija conocida que es el indazol, y cuando se dan los significados de los sustituyentes R^1 , R^2 , R^3 , R^7 , R^8 , R^9 , R^{10} , R^{11} , se hacen de una manera ambigua, designándolos de la manera mas genérica posible, tal como: "arilo", "heteroarilo sustituido o no sustituido". "alquilo", "alquenilo", "cicloalquilo", "alquilideno", "alcoxilo", "heterocicloalquilo", "cicloalquilo" estos son términos ambiguos e inaceptables en las reivindicaciones, porque solo con cada sustituyente designado de esa manera ambigua, comprende un número incalculable de estructuras, y si se sigue con las posibles combinaciones por cada uno de los otros sustituyentes, podremos ver cuan especulativo es. Realmente no hay una estructura representativa de los compuestos reclamados, que se pueda considerar que delimita inequívocamente el alcance de las reivindicaciones, por lo cual no puede ser considerado que satisface el requerimiento de claridad y que este perfectamente definida la materia para la cual se solicita la protección mediante patente, tal como lo establece el artículo 30 de la Decisión 486 de la comisión de la Comunidad Andina.

-El significado del sustituyente X, no esta delimitado, porque los términos "arilo, heteroarilo, alquilideno, NH-dialquiloamida, NH-(cicloalquilo), NH-(heterocicloalquilo)", y las definiciones similares, no determinan, ni delimitan inequívocamente ningún sustituyente, porque el alcance no esta limitado y no son razonable las generalizaciones.

-Además las reivindicaciones reclaman "**metabolitos**", "**prodrogas**"; son expresiones funcionales, es definir la materia en términos de propiedades deseadas, en lugar de indicar la materia definida en términos técnicos exactos, y por demás estos compuestos reclamados, no aparece ningún profármaco, o alguna estructura de metabolito o algún proceso para obtener el metabolito, en la descripción; por lo tanto es inaceptable en las reivindicaciones, por no estar enteramente sustentado en la descripción, y además ser desconocida e indefinida la materia que se reclama, con esos términos.

Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 de la Comisión de la Comunidad Andina establece en su inciso d) que no serán patentables: *"los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*.

Las reivindicaciones 14 a 17 se pretenden proteger un método para tratamiento del cuerpo humano o animal, por lo tanto están inmersas bajo el alcance del artículo 20 de la Decisión 486.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Se realizó la búsqueda del estado de la técnica con fecha anterior a la fecha de presentación de la primera solicitud, de la cual se reivindica prioridad, 02 de julio de 1999. Consultada la fuente de información con que cuenta este despacho se encontró los siguientes documentos:

No.	Documento No.	Título	*Fecha de Publicación
D1	CA2389918	Composes D'indazolesubtitue utile comme intermediaires	13-nov-1997
D2	EP0816357	Substituted Indazole derivatives	07-ene-1998
D3	US5.843.975	Oxazolidinone derivatives, their preparation and therapeutical use	01-dic-1998

D4	WO9809961	Indazole derivatives and their use as inhibitors of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF)	12-mar-1998
D5	WO9742174	Substituted Indazole derivatives and their use as inhibitors of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF)	13-nov-1997
D6	WO974972	Indazole derivatives and their use as inhibitors of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF)	31-dic-1997
D7	WO9421630	Antipsychotic Indazole derivatives	29-sep-1994
D8	US5,760,028	Integrin Receptor ANtagonists	02-jun-1998
D9	WO9703069	Heterocyclic compounds and pharmaceutical compositions containing them	30-ene-1997

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece:
"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."

En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

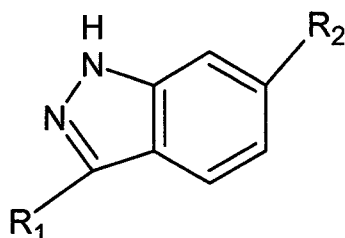
Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica."* *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la

solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

La solicitud en estudio reclama de un compuesto de formula (I) 3, 5 disustituidos de indazol:



-Solamente se adjuntaron 9 anterioridades, de todas las posibles que afectan la novedad por la forma amplia y especulativa como reclaman la materia en la presente invención.

-D1 a D9 comprenden derivados 3,6 disustituidos de indazol, comprenden los sustituyentes sobre las posiciones 3 y 6 del biciclo de indazol, y que los significados de dichos sustituyentes caen dentro de la materia reclamada como nueva en la solicitud en estudio. Por lo tanto la solicitud en estudio no es nueva.

-Además tal como puede verse por ejemplo en D9 los compuestos específicos preferidos de esa invención, son compuestos particulares destruyen la novedad de los compuestos reclamados en la solicitud en estudio. Véase toda la anterioridad particularmente las páginas 12 y 13.

Cuando una solicitud esta afectada su novedad, obviamente no posee nivel inventivo.

En conclusión los requisitos de Patentabilidad de la presente solicitud están afectadas así:

No.	Documento	Reivindicaciones	Requisito que afecta
D1.	CA2389918	1 a 17	Novedad
D2	EP0816357	1 a 17	Novedad
D3	US 5843975	1 a 17	Novedad
D4	WO9809961	1 a 17	Novedad
D5	WO9742174	1 a 17	Novedad
D6	WO9749702	1 a 17	Novedad
D7	WO9421630	1 a 17	Novedad
D8	US 5760028	1 a 17	Novedad
D9	WO9703069	1 a 17	Novedad

Notifíquese conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5° del título 1° de la Circular Única n°.10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL.
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 15 JUN. 2016

CONCEPTO TÉCNICO No. 940	EXAMINADOR TÉCNICO Código: 202012
-----------------------------	--------------------------------------

DI

596

(19)  Canadian
Intellectual Property
Office

An Agency of
Industry Canada

Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

(11) CA 2 389 918

(13) A1

(40) 13.11.1997
(43) 13.11.1997

Todo

(12)

(21) 2 389 918

(51) Int. Cl.⁷:

C07D 231/54

(22) 01.04.1997

(30) 60/016,861 US 03.05.1996

235 East 42nd Street, NEW YORK, XX (US).

(60) 25.07.2002

(62) 2252982

(72)

MARFAT, ANTHONY (US).

(71)

PFIZER INC.,

(74)

SMART & BIGGAR

(54) COMPOSES D'INDAZOLE SUBSTITUE UTILE COMME INTERMEDIAIRES

(54) SUBSTITUTED INDAZOLE COMPOUNDS USEFUL AS INTERMEDIATES

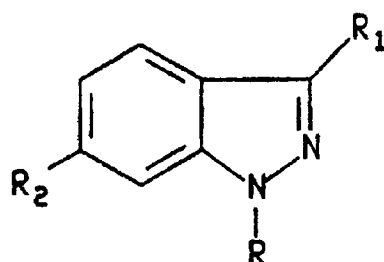
(57)

Disclosed are novel 1H-indazole compounds of the formula: (see formula I) wherein R is H, alkyl, cycloalkyl(alkyl), alkoxyalkyl, alkenyl, heterocycl(alkyl) or -(Z')b(Z'')c aryl in which Z' is alkylene or alkenylene, Z'' is O, S, SO₂ or NR₉, b and c are each 0 or 1, R₁ is H, alkyl, alkenyl, phenyl or cycloalkyl(alkyl), R₉ is H or alkyl and X is Br, alkoxy carbonyl, cyanomethyl, carboxyl, hydroxymethyl or formyl. The compounds are useful as intermediates for producing selective inhibitors of phosphodiesterase (PDE) type IV and tumor necrosis factor (TNF).

Summary of the Invention

The present invention relates to compounds of the formula I

5



I

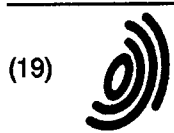
10 and to pharmaceutically acceptable salts thereof, wherein:

R is hydrogen, C₁-C₆ alkyl, -(CH₂)_n(C₃-C₇ cycloalkyl) wherein n is 0 to 2, (C₁-C₆ alkoxy)C₁-C₆ alkyl, C₂-C₆ alkenyl, -(CH₂)_n(C₃-C₉ heterocyclyl) wherein n is 0 to 2, or -(Z')_b(Z'')_c(C₆-C₁₀ aryl) wherein b and c are independently 0 or 1, Z' is C₁-C₆ alkylene or C₂-C₆ alkenylene, and Z'' is O, S, SO₂, or NR₉, and wherein said alkyl, alkenyl, 15 alkoxyalkyl, heterocyclyl, and aryl moieties of said R groups are optionally substituted by 1 to 3 substituents independently selected from halo, hydroxy, C₁-C₅ alkyl, C₂-C₅ alkenyl, C₁-C₅ alkoxy, C₃-C₆ cycloalkoxy, trifluoromethyl, nitro, CO₂R₉, C(O)NR₉R₁₀, NR₉R₁₀ and SO₂NR₉R₁₀;

20 R₁ is hydrogen, C₁-C₇ alkyl, C₂-C₇ alkenyl, phenyl, C₃-C₇ cycloalkyl, or (C₃-C₇ cycloalkyl)C₁-C₂ alkyl, wherein said alkyl, alkenyl and phenyl R₁ groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

D2

538



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 0 816 357 A1**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
07.01.1998 Bulletin 1998/02

(51) Int. Cl.⁶: **C07D 401/14**, A61K 31/44,
C07D 401/06

(21) Application number: **97304083.5**

// (C07D401/14, 231:00,
213:00, 213:00)

(22) Date of filing: **11.06.1997**

(84) Designated Contracting States:
**AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC
NL PT SE**

(72) Inventor: **Marfat, Anthony**
Mystic, Connecticut 06355 (US)

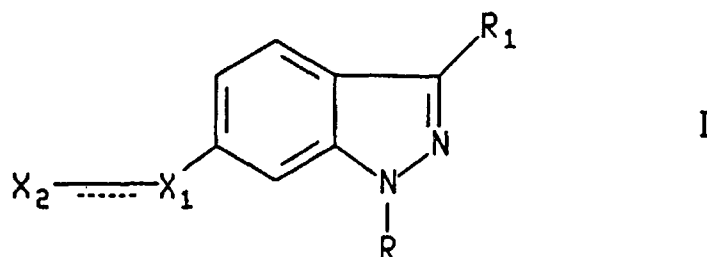
(30) Priority: **27.06.1996 US 21072 P**

(74) Representative:
Hayles, James Richard
Pfizer Limited,
Patents Department,
Ramsgate Road
Sandwich Kent CT13 9NJ (GB)

(71) Applicant: **PFIZER INC.**
New York, N.Y. 10017 (US)

(54) **Substituted indazole derivatives**

(57) The invention relates to compounds of the formula



and to pharmaceutically acceptable salts thereof, wherein the broken line in formula I indicates a single or double bond, and wherein R, R₁, X₁ and X₂ are as defined herein. The invention further relates to pharmaceutical compositions containing the compounds of formula I, and to methods of inhibiting phosphodiesterase type IV or the production of tumor necrosis factor in a mammal by administering the compounds of formula I to said mammal.

EP 0 816 357 A1

EP 0 816 357 A1

Description

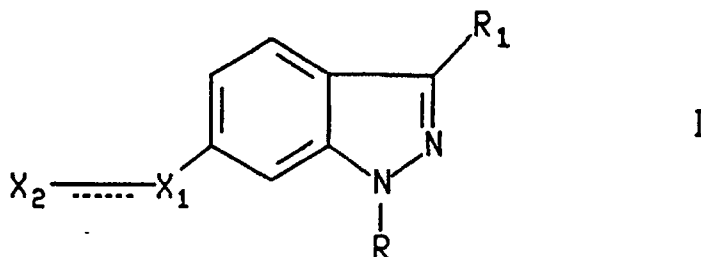
This invention relates to novel indazole analogs that are selective inhibitors of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF), and as such are useful in the treatment of asthma, arthritis, bronchitis, chronic obstructive airway disease, psoriasis, allergic rhinitis, dermatitis, and other inflammatory diseases, central nervous system disorders such as depression and multi-infarct dementia, AIDS, septic shock and other diseases involving the production of TNF. This invention also relates to a method of using such compounds in the treatment of the foregoing diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

Since the recognition that cyclic adenosine phosphate (AMP) is an intracellular second messenger (E.W. Sutherland, and T. W. Rall, *Pharmacol. Rev.*, 12, 265, (1960)), inhibition of the phosphodiesterases has been a target for modulation and, accordingly, therapeutic intervention in a range of disease processes. More recently, distinct classes of PDE have been recognized (J. A. Beavo *et al.*, *Trends in Pharm. Sci. (TIPS)*, 11, 150, (1990)), and their selective inhibition has led to improved drug therapy (C. D. Nicholson, M. S. Hahid, *TIPS*, 12, 19, (1991)). More particularly, it has been recognized that inhibition of PDE type IV can lead to inhibition of inflammatory mediator release (M. W. Verghese *et al.*, *J. Mol. Cell Cardiol.*, 12 (Suppl. II), S 61, (1989)) and airway smooth muscle relaxation (T.J. Torphy in "Directions for New Anti-Asthma Drugs," eds S.R. O'Donnell and C. G. A. Persson, 1988, 37 Birkhauser-Verlag). Thus, compounds that inhibit PDE type IV, but which have poor activity against other PDE types, would inhibit the release of inflammatory mediators and relax airway smooth muscle without causing cardiovascular effects or antiplatelet effects. It has also been disclosed that PDE IV inhibitors are useful in the treatment of diabetes insipidus (*Kidney Int.* 37:362, 1990; *Kidney Int.* 35:494) and central nervous system disorders such as depression and multi-infarct dementia (PCT international application WO 87/06576 (published November 5, 1987)).

TNF is recognized to be involved in many infectious and auto-immune diseases (W. Friers, *Fed. of Euro. Bio. Soc. (FEBS) Letters*, 285, 199, (1991)). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C. E. Spooner *et al.*, *Clinical Immunology and Immunopathology*, 62, S11, (1992)).

Summary of the Invention

The present invention relates to compounds of the formula I



and to pharmaceutically acceptable salts thereof, wherein:

the broken line indicates a single or double bond;

X₁ is -CR₂R₃ where said broken line indicates a single bond or -CR₃ where said broken line indicates a double bond;

X₂ is -CR₅R₇R₈ or -C(=NOR₁₁)R₁₂ where said broken line indicates a single bond or -CR₇R₈ where said broken line indicates a double bond;

R is H, C₁-C₆ alkyl, -(CH₂)_m(C₃-C₇ cycloalkyl), -(CH₂)_m(C₃-C₉ heterocyclyl), wherein m is 0 to 2, (C₁-C₆ alkoxy)C₁-C₆ alkyl, C₂-C₆ alkenyl, or -(Z₁)_b(Z₂)_c(C₆-C₁₀ aryl) wherein b and c are independently 0 or 1, Z₁ is C₁-C₆ alkylene or C₂-C₆ alkenylene, and Z₂ is O, S, SO₂, or NR₅, and wherein said R groups are optionally substituted by one or more substituents independently selected from the group consisting of halo, hydroxy, C₁-C₅ alkyl, C₂-C₅ alkenyl, C₁-C₅ alkoxy, C₃-C₆ cycloalkoxy, trifluoromethyl, nitro, -CO₂R₅, -C(O)NR₅R₆, -NR₅R₆ and -SO₂NR₅R₆;

R₁ is H, C₁-C₇ alkyl, C₂-C₃ alkenyl, phenyl, C₃-C₇ cycloalkyl, or (C₃-C₇ cycloalkyl)C₁-C₂ alkyl, wherein said alkyl, alkenyl and phenyl R₁ groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

R₂ is H, hydroxy, halo or -OR₃;

each R₃ is independently selected from the group consisting of cyano, cyanomethyl, benzyloxy, R₅, -CO₂R₅, -

D3

600



US005843975A

United States Patent [19]
Jegham et al.

[11] **Patent Number:** **5,843,975**
[45] **Date of Patent:** **Dec. 1, 1998**

[54] **OXAZOLIDINONE DERIVATIVES, THEIR
PREPARATION AND THERAPEUTICAL USE**

[58] **Field of Search** 548/212, 231;
514/373, 376

[75] **Inventors:** **Samir Jegham**, Argenteuil; **Frédéric
Puech**, Rueil Malmaison; **Philippe
Burnier**, Maisons Laffitte, all of France

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,036,090	7/1991	Jarreau et al.	514/376
5,036,091	7/1991	Jarreau et al.	514/376
5,171,747	12/1992	Jarreau et al.	514/376
5,173,490	12/1992	Peglion et al.	514/254
5,182,296	1/1993	Nakai et al.	514/376
5,196,543	3/1993	Jarreau et al.	548/232
5,235,063	8/1993	Jarreau et al.	548/232
5,332,754	7/1994	Nakai et al.	514/376

[73] **Assignee:** **Synthelabo**, Le Plessis Robinson,
France

[21] **Appl. No.:** **973,246**

[22] **PCT Filed:** **May 28, 1996**

[86] **PCT No.:** **PCT/FR96/00792**

§ 371 Date: **Dec. 2, 1997**

§ 102(e) Date: **Dec. 2, 1997**

[87] **PCT Pub. No.:** **WO96/38444**

PCT Pub. Date: **Dec. 5, 1996**

[30] **Foreign Application Priority Data**

Jun. 2, 1995	[FR]	France	95 06563
Jun. 2, 1995	[FR]	France	95 06564

[51] **Int. Cl.⁶** **A61K 31/425**; C01D 413/04

[52] **U.S. Cl.** **514/376**; 514/373; 548/212;
548/231

Primary Examiner—Johann Richter

Assistant Examiner—Laura R. C. Lutz

Attorney, Agent, or Firm—Jacobson, Price, Holman &
Stern, PLLC

[57] **ABSTRACT**

The present invention relates to isoindole derivatives, and more particularly to 5-(hydroxymethyl)oxazolidine-2-one derivatives which are substituted at the 3 position by an indazole, benzisoxazole or benzisothiazole ring system, to a process for their preparation and to their application in therapy.

11 Claims, No Drawings

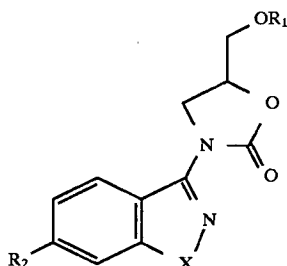
1

OXAZOLIDINONE DERIVATIVES, THEIR PREPARATION AND THERAPEUTICAL USE

This application is a 371 of PCT/FR96/00292 filed May 28, 1996.

The present invention relates to isoindole derivatives, and more particularly to 5-(hydroxymethyl)oxazolidine-2-one derivatives which are substituted at the 3 position by an indazole, benzisoxazole or benzisothiazole ring system, to a process for their preparation and to their application in therapy.

The compounds of the invention correspond to the general formula (I)



in which:

X represents an oxygen atom, a sulphur atom or a group NR, R being a hydrogen atom or a linear or branched C_1-C_4 alkyl chain,

R_1 represents a hydrogen atom or a methyl group, and

R_2 represents:

- (i) a group R_3O in which R_3 represents alternatively a hydrogen atom, or a benzyl group which is optionally substituted with a halogen atom or with a nitro or methylenedioxy group, or represents a methoxyethyl, butyl, 4,4,4-trifluorobutyl, 4,4,4-trifluoro-3-hydroxybutyl or 4,4,4-trifluorobut-2-enyl group, or (ii) a group $-CH=CH-R_4$ or $-CH_2-CH_2-R_4$, in which R_4 represents a hydrogen atom or a phenyl, 3,3,3-trifluoropropyl or 3,3,3-trifluoro-2-hydroxypropyl group.

The compounds of formula (I) comprise one or two asymmetric carbon atoms. They can therefore exist in the form of enantiomers or diastereoisomers. These various forms and their mixtures, including the racemic mixtures, are part of the invention.

The compounds of formula (I) in which X is an oxygen atom and R_2 represents a group $-CH=CH-R_4$, with the exception of compounds in which R_4 is a hydrogen atom, exist in the form of cis or trans isomers. These forms and their mixtures are part of the invention.

The compounds of formula (I) in which R_2 represents a group OR_3 in which R_3 represents the 4,4,4-trifluorobut-2-enyl group exist in the form of cis or trans isomers. These forms and their mixtures are part of the invention.

Preferred compounds are those for which:

X represents an oxygen atom, a sulphur atom or a group NR, R being a hydrogen atom or a linear or branched C_1-C_4 alkyl chain,

R_1 represents a methyl group or a hydrogen atom, and

R_2 represents a group R_3O in which R_3 represents alternatively a hydrogen atom, or a benzyl group which is optionally substituted with a halogen atom or with a nitro or methylenedioxy group, or represents a methoxyethyl, butyl, 4,4,4-trifluorobutyl, 4,4,4-trifluoro-3-hydroxybutyl or 4,4,4-trifluorobut-2-enyl group,

2

in the form of enantiomers or diastereoisomers, or of mixtures of these various forms, including racemic mixtures.

Other preferred compounds are those for which:

X represents an oxygen atom, a sulphur atom or a group NR, R being a hydrogen atom or a linear or branched C_1-C_4 alkyl chain,

R_1 represents a methyl group or a hydrogen atom, and

R_2 represents a group $-CH=CH-R_4$ or $-CH_2-CH_2-R_4$, in which R_4 represents a hydrogen atom, or a phenyl, 3,3,3-trifluoropropyl or 3,3,3-trifluoro-2-hydroxypropyl group,

in the form of enantiomers or diastereoisomers, or of mixtures of these various forms, including racemic mixtures.

The compounds of choice are those for which:

X represents an oxygen atom,

R_1 represents a methyl group or a hydrogen atom, and

R_2 represents:

- (i) a group R_3O in which R_3 represents alternatively a hydrogen atom, or a benzyl group which is optionally substituted with a halogen atom or with a nitro or methylenedioxy group, or represents a methoxyethyl, butyl, 4,4,4-trifluorobutyl, 4,4,4-trifluoro-3-hydroxybutyl or 4,4,4-trifluorobut-2-enyl group, or
- (ii) a group $-CH=CH-R_4$ or $-CH_2-CH_2-R_4$, in which R_4 represents a hydrogen atom, or a phenyl, 3,3,3-trifluoropropyl or 3,3,3-trifluoro-2-hydroxypropyl group,

in the form of enantiomers or diastereoisomers, or of mixtures of these various forms, including racemic mixtures.

Among the latter, mention may be made of compounds for which:

X represents an oxygen atom,

R_1 represents a methyl group or a hydrogen atom, and

R_2 represents alternatively a hydroxyl group, or a phenylmethoxy group which is optionally substituted with a halogen atom or with a nitro or methylenedioxy group, or represents a 4,4,4-trifluorobutoxy group or a 4,4,4-trifluoro-3-hydroxybutoxy group,

in the form of enantiomers or diastereoisomers, or of mixtures of these various forms, including racemic mixtures, and, very particularly, mention may be made of (S)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one.

The compounds of formula (I) in which R_1 is a methyl group and R_2 is a group OR_3 can be prepared according to the process represented in scheme 1. According to this process, the isoindole derivative of formula (II) is treated with one of the 4(R) or 4(S) isomers of 4-methoxymethyl-1,3-dioxolan-2-one of formula (IIIa) in the presence of potassium carbonate in order to obtain the 5(S) or 5(R) isomer of the compound of formula (Ia) according to the invention. It is then possible to debenzylate the compound (Ia) by catalytic hydrogenation under conditions which are conventional to the person skilled in the art, or with the aid of a Lewis acid such as aluminium chloride, in order to obtain the 5(S) or 5(R) isomer of the compound of formula (Ib) according to the invention. Subsequently, it is possible to treat the compound (Ib) either with a compound of formula R_3Y in which R_3 is defined as in formula (I) above, with the exception of the meanings hydrogen and unsubstituted benzyl, and Y is a leaving group, such as a chlorine or bromine atom or a tosyloxy group, in the presence of potassium carbonate, or with a compound of formula R_3OH in which R_3 is defined as above, in the presence of triphenylphosphine and diethyl azodicarboxylate, in order to

D4

602



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

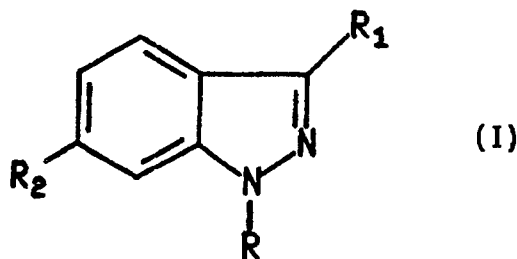
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/12, A61K 31/415, 31/44, C07D 409/04, 231/56	A1	(11) International Publication Number: WO 98/09961
		(43) International Publication Date: 12 March 1998 (12.03.98)
(21) International Application Number: PCT/IB97/01023 (22) International Filing Date: 25 August 1997 (25.08.97) (30) Priority Data: 60/025,446 4 September 1996 (04.09.96) US (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): MARFAT, Anthony [US/US]; 333 Lantern Hill Road, Mystic, CT 06355 (US). (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: INDAZOLE DERIVATIVES AND THEIR USE AS INHIBITORS OF PHOSPHODIESTERASE (PDE) TYPE IV AND THE PRODUCTION OF TUMOR NECROSIS FACTOR (TNF)

(57) Abstract

The invention relates to compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein R, R₁, and R₂, are as defined herein. The invention further relates to pharmaceutical compositions containing, and methods of using, the compounds of formula (I), or acceptable salts thereof, for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal. The invention also relates to intermediates that are useful in the preparation of the compounds of formula (I).



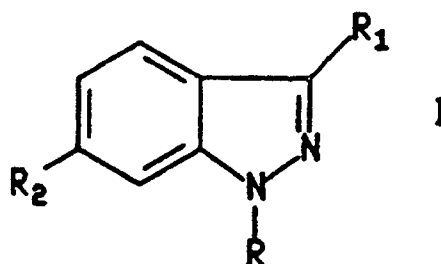
-2-

such as depression and multi-infarct dementia (PCT international application WO 92/19594 (published November 12, 1992)).

TNF is recognized to be involved in many infectious and auto-immune diseases (W. Friers, Fed. of Euro. Bio. Soc. (FEBS) Letters, 285, 199, (1991)). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C. E. Spooner et al., Clinical Immunology and Immunopathology, 62, S11, (1992)).

Summary of the Invention

The present invention relates to compounds of the formula I



and to pharmaceutically acceptable salts thereof, wherein:

R is H, C₁-C₈ alkyl, -(CH₂)_m (5 to 10 membered heterocyclyl) wherein m is 0 to 2, (C₁-C₈ alkoxy)C₁-C₈ alkyl, C₂-C₈ alkenyl, or -(Z₁)_b(Z₂)_c(C₆-C₁₀ aryl) wherein b and c are independently 0 or 1, Z₁ is C₁-C₈ alkylene or C₂-C₈ alkenylene, and Z₂ is O, S, SO₂, or NR₁₂, and wherein said R groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₁-C₈ alkoxy, trifluoromethyl, nitro, -CO₂R₁₂, -C(O)NR₁₂R₁₃, -NR₁₂R₁₃ and -SO₂NR₁₂R₁₃:

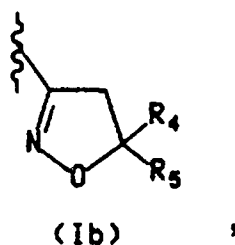
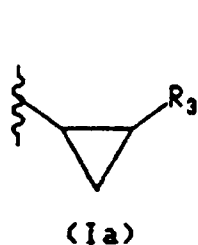
(R₁) is H, C₁-C₈ alkyl, C₂-C₈ alkenyl, or phenyl, wherein said alkyl, alkenyl and phenyl R₁ groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

(R₂) is R₁₀, -C(O)NR₁₂(CHR₁₂)_mC(O)NR₁₂O(CH₂)_q(C₆-C₁₀ aryl), -C(=NR₂₂)NH(CH₂)_p(C₆-C₁₀ aryl), -C(O)NR₆(CHR₁₂)_mC(O)NR₁₂(CH₂)_pOR₁₂, -C(O)NR₁₂(CHR₁₂)_mS(C₁-C₄ alkyl), -C(=NOC(O)R₂₂)R₂₂, -CR₁₇R₁₈CHR₂₂NR₉SO₂(CH₂)_pA, -CR₁₇R₁₈CHR₂₂NR₉P(O)(OR₁₂)C(O)(C₁-C₄ alkyl), -CR₁₇R₁₈CHR₂₂NR₉P(O)(C₁-C₄ alkoxy)₂, -Z₃-R₇, or -(CR₁₇R₁₈)_mNR₉(C(O))_pR₁₀ wherein p is 0 to 2, m is 1 to 6, and q is 1 or 2;

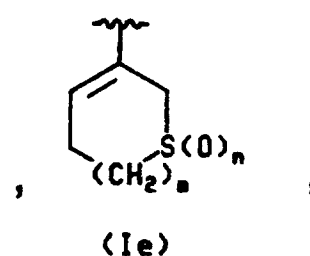
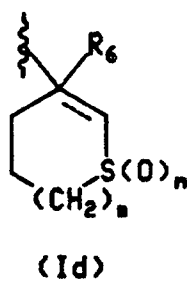
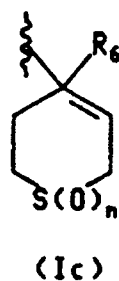
-3-

or R_2 is

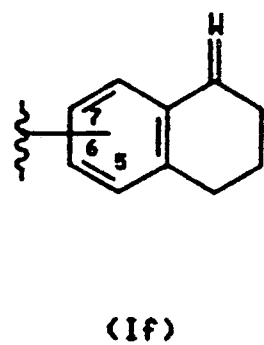
5



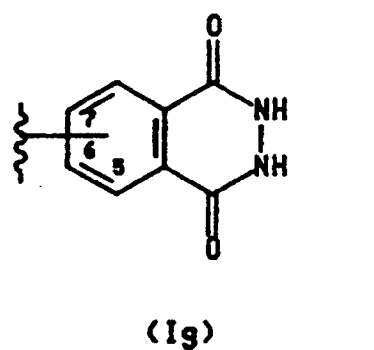
10



15



20

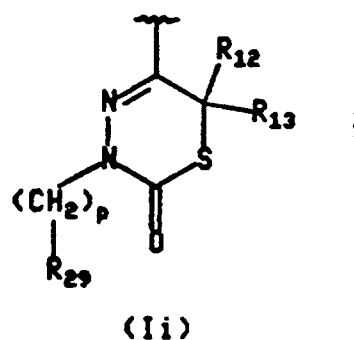


25



or

30



DS

605



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

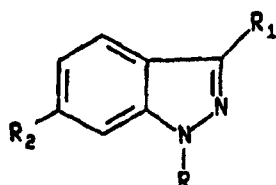
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 231/56, A61K 31/415, C07D 409/08		A1	(11) International Publication Number: WO 97/42174
			(43) International Publication Date: 13 November 1997 (13.11.97)
(21) International Application Number: PCT/IB97/00323		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 1 April 1997 (01.04.97)		Published With international search report.	
(30) Priority Data: 60/016,861 3 May 1996 (03.05.96) US			
(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).			
(72) Inventor; and (75) Inventor/Applicant (for US only): MARFAT, Anthony [US/US]; 333 Lantern Hill Road, Mystic, CT 06355 (US).			
(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).			

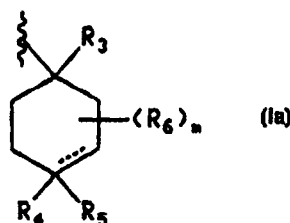
(54) Title: **SUBSTITUTED INDAZOLE DERIVATIVES AND THEIR USE AS INHIBITORS PHOSPHODIESTERASE (PDE) TYPE IV AND THE PRODUCTION OF TUMOR NECROSIS FACTOR (TNF)**

(57) Abstract

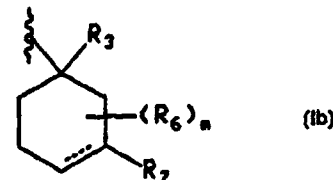
The invention relates to compounds of formula (I), and to pharmaceutically acceptable salts thereof, wherein R and R₁ are as defined herein. R₂ is selected from the group consisting of (Ia), (Ib), (Ic) and (Id). The invention further relates to intermediates for the preparation of the compounds of formula (I), and to pharmaceutical compositions containing, and methods of using, the compounds of formula (I), or pharmaceutically acceptable salts thereof, for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal.



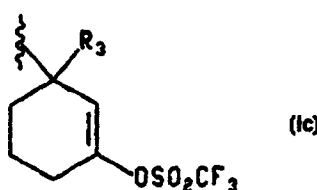
(I)



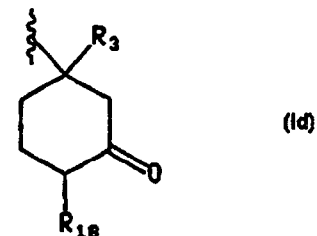
(Ia)



(Ib)



(Ic)

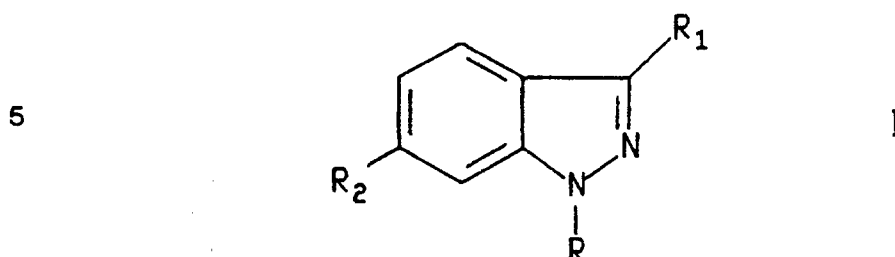


(Id)

-2-

Summary of the Invention

The present invention relates to compounds of the formula I



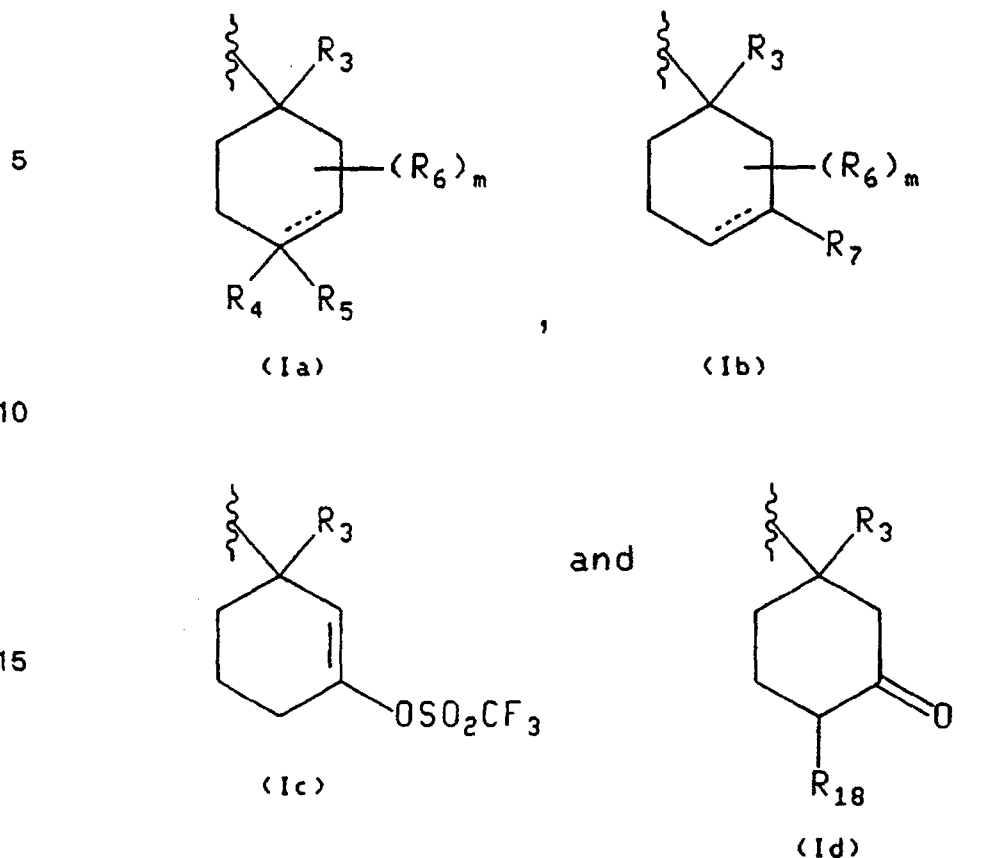
- 10 and to pharmaceutically acceptable salts thereof, wherein:

R is hydrogen, C₁-C₆ alkyl, -(CH₂)_n(C₃-C₇ cycloalkyl) wherein n is 0 to 2, (C₁-C₆ alkoxy)C₁-C₆ alkyl, C₂-C₆ alkenyl, -(CH₂)_n(C₃-C₉ heterocyclyl) wherein n is 0 to 2, or -(Z')_b(Z'')_c(C₆-C₁₀ aryl) wherein b and c are independently 0 or 1, Z' is C₁-C₆ alkylene or C₂-C₆ alkenylene, and Z'' is O, S, SO₂, or NR₉, and wherein said alkyl, alkenyl, alkoxyalkyl, heterocyclyl, and aryl moieties of said R groups are optionally substituted by 1 to 3 substituents independently selected from halo, hydroxy, C₁-C₅ alkyl, C₂-C₅ alkenyl, C₁-C₅ alkoxy, C₃-C₆ cycloalkoxy, trifluoromethyl, nitro, CO₂R₉, C(O)NR₉R₁₀, NR₉R₁₀ and SO₂NR₉R₁₀;

- 20 R₁ is hydrogen, C₁-C₇ alkyl, C₂-C₃ alkenyl, phenyl, C₃-C₇ cycloalkyl, or (C₃-C₇ cycloalkyl)C₁-C₂ alkyl, wherein said alkyl, alkenyl and phenyl R₁ groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

-3-

R_2 is selected from the group consisting of



wherein the dashed line in formulas (Ia) and (Ib) represent a single or double bond;

m is 0 to 4;

R_3 is H, halo, cyano, C_1 - C_4 alkyl optionally substituted by 1 to 3 halo groups, $CH_2NHC(O)C(O)NH_2$, cyclopropyl optionally substituted by R_{11} , R_{17} , CH_2OR_9 , NR_9R_{10} , $CH_2NR_9R_{10}$, CO_2R_9 , $C(O)NR_9R_{10}$, $C\equiv CR_{11}$, $C(Z)H$ or $CH=CR_{11}R_{11}$;

25

R_4 is H, $C(Y)R_{14}$, CO_2R_{14} , $C(Y)NR_{17}R_{14}$, CN, $C(NR_{17})NR_{17}R_{14}$, $C(NOR_9)R_{14}$, $C(O)NR_9NR_9C(O)R_9$, $C(O)NR_9NR_{17}R_{14}$, $C(NOR_{14})R_9$, $C(NR_9)NR_{17}R_{14}$, $C(NR_{14})NR_9R_{10}$, $C(NCN)NR_{17}R_{14}$, $C(NCN)S(C_1-C_4 \text{ alkyl})$, $CR_9R_{10}OR_{14}$, $CR_9R_{10}SR_{14}$, $CR_9R_{10}S(O)_nR_{15}$, wherein n is 0 to 2, $CR_9R_{10}NR_{14}R_{17}$, $CR_9R_{10}NR_{17}SO_2R_{15}$, $CR_9R_{10}NR_{17}C(Y)R_{14}$, $CR_9R_{10}NR_{17}CO_2R_{15}$, $CR_9R_{10}NR_{17}C(Y)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(NCN)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(CR_9NO_2)S(C_1-C_4 \text{ alkyl})$, $CR_9R_{10}CO_2R_{15}$, $CR_9R_{10}C(Y)NR_{17}R_{14}$, $CR_9R_{10}C(NR_{17})NR_{17}R_{14}$, $CR_9R_{10}CN$, $CR_9R_{10}C(NOR_{10})R_{14}$, $CR_9R_{10}C(NOR_{14})R_{10}$, $CR_9R_{10}NR_{17}C(NR_{17})S(C_1-C_4 \text{ alkyl})$, $CR_9R_{10}NR_{17}C(NR_{17})NR_{17}R_{14}$,

30

DC

608



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

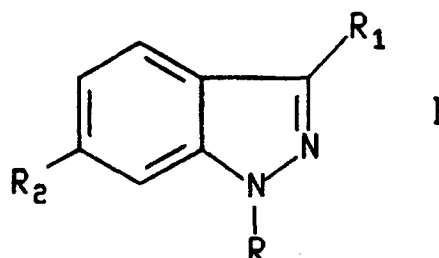
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 403/04, A61K 31/415		A1	(11) International Publication Number: WO 97/49702
			(43) International Publication Date: 31 December 1997 (31.12.97)
(21) International Application Number: PCT/IB97/00630 (22) International Filing Date: 2 June 1997 (02.06.97) (30) Priority Data: 60/020,385 25 June 1996 (25.06.96) US (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): MARFAT, Anthony [US/US]; 333 Lantern Hill Road, Mystic, CT 06355 (US). (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: SUBSTITUTED INDAZOLE DERIVATIVES AND THEIR USE AS PHOSPHODIESTERASE (PDE) TYPE IV AND TUMOR NECROSIS FACTOR (TNF) INHIBITORS			
(57) Abstract The invention relates to compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein R, R ₁ and R ₂ are as defined herein. The invention further relates to pharmaceutical compositions containing, and methods of using, the compounds of formula (I), or acceptable salts thereof, for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal.			
		(I)	

-2-

The present invention relates to compounds of the formula I

5



and to pharmaceutically acceptable salts thereof, wherein:

- 10 R is H, C₁-C₆ alkyl, -(CH₂)_m(C₃-C₇ cycloalkyl), -(CH₂)_m(C₃-C₉ heterocyclyl), wherein m is 0 to 2, (C₁-C₆ alkoxy)C₁-C₆ alkyl, C₂-C₆ alkenyl, or -(Z₁)_b(Z₂)_c(C₆-C₁₀ aryl) wherein b and c are independently 0 or 1, Z₁ is C₁-C₆ alkylene or C₂-C₆ alkenylene, and Z₂ is O, S, SO₂, or NR₁₀, and wherein said R groups are optionally substituted by one or more substituents independently selected from the group consisting of halo,
- 15 hydroxy, C₁-C₅ alkyl, C₂-C₆ alkenyl, C₁-C₅ alkoxy, C₃-C₆ cycloalkoxy, trifluoromethyl, nitro, -CO₂R₁₀, -C(O)NR₁₀R₁₁, -NR₁₀R₁₁, and -SO₂NR₁₀R₁₁;

- R₁ is H, C₁-C₇ alkyl, C₂-C₃ alkenyl, phenyl, C₃-C₇ cycloalkyl, or (C₃-C₇ cycloalkyl)C₁-C₂ alkyl, wherein said alkyl, alkenyl and phenyl R₁ groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of
- 20 methyl, ethyl, trifluoromethyl, and halo;

- R₂ is 2-oxo-4-pyrrolyl, pyrazolyl, 2-oxo-3,4-dihydro-5-pyrimidyl, 2-oxo-3,4-dihydro-4-pyrimidyl, 2-oxo-tetrahydro-4-pyrimidyl, 2-oxo-tetrahydro-5-pyrimidyl, 2-oxo-4-pyrimidyl, or 2-oxo-5-pyrimidyl, wherein each of said R₂ groups is optionally substituted by 1 to 4 R₆ groups;
- 25

07

610



PCT

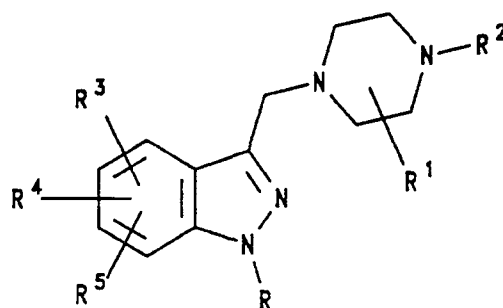
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 403/06, A61K 31/495 // (C07D 403/06, 231:00, 295:00)		A1	(11) International Publication Number: WO 94/21630 (43) International Publication Date: 29 September 1994 (29.09.94)
(21) International Application Number: PCT/GB94/00504 (22) International Filing Date: 14 March 1994 (14.03.94) (30) Priority Data: 9305623.2 18 March 1993 (18.03.93) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BAKER, Raymond [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). KULAGOWSKI, Janusz, Jozef [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). LEESON, Paul, David [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SMITH, Adrian, Leonard [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: THOMPSON, John; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: ANTIPSYCHOTIC INDAZOLE DERIVATIVES			
(57) Abstract A class of 1H-indazole derivatives, substituted at the 3-position by a substituted piperazinylmethyl moiety, are antagonists of dopamine receptor subtypes within the brain, having a selective affinity for the dopamine D ₄ receptor subtype over other dopamine receptor subtypes, and are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia whilst manifesting fewer side-effects than those associated with classical neuroleptic drugs.			

CLAIMS:

1. The use of a compound of formula I, or a
pharmaceutically acceptable salt thereof or a prodrug
5 thereof:



(I)

wherein

R represents hydrogen or C₁₋₆ alkyl;

R¹ represents hydrogen, or an optionally
substituted C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆
20 alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl,
aryl, aryl(C₁₋₆)alkyl, aryl(C₁₋₆)alkoxy,
aryl(C₂₋₆)alkenyl, aryl(C₂₋₆)alkynyl, heteroaryl,
heteroaryl(C₁₋₆)alkyl, heteroaryl(C₂₋₆)alkenyl or
heteroaryl(C₂₋₆)alkynyl group;

25 R² represents an optionally substituted C₁₋₆
alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇
cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl,
aryl(C₁₋₆)alkyl, aryl(C₁₋₆)alkoxy, aryl(C₂₋₆)alkenyl,
aryl(C₂₋₆)alkynyl, heteroaryl, heteroaryl(C₁₋₆)alkyl,
30 heteroaryl(C₂₋₆)alkenyl or heteroaryl(C₂₋₆)alkynyl group;

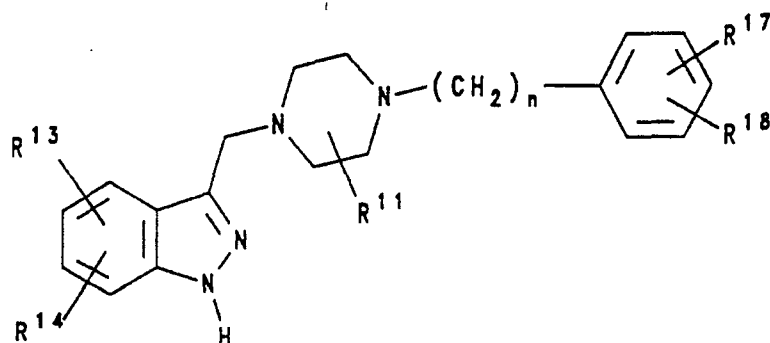
R³, R⁴ and R⁵ independently represent hydrogen,
hydrocarbon, a heterocyclic group, halogen, cyano,
trifluoromethyl, nitro, -OR^a, -SR^a, -SOR^a, -SO₂R^a,
-SO₂NR^aR^b, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -COR^a, -CO₂R^a or
35 -CONR^aR^b; and

- 51 -

R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group; for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders.

5

2. The use as claimed in claim 1 of a compound represented by formula IIA, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIA)

wherein

20

n is zero, 1, 2 or 3;

R^{11} represents hydrogen or C_{1-6} alkyl;

25

R^{13} and R^{14} independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or C_{2-6} alkylcarbonyl; or R^{13} and R^{14} , when situated on adjacent carbon atoms, together represent methylenedioxy; and

30

R^{17} and R^{18} independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or C_{2-6} alkylcarbonyl; or R^{17} and R^{18} , when situated on adjacent carbon atoms, together represent methylenedioxy.

D8



613

US005760028A

United States Patent [19]

Jadhav et al.

[11] **Patent Number:** 5,760,028[45] **Date of Patent:** Jun. 2, 1998[54] **INTEGRIN RECEPTOR ANTAGONISTS**

[75] **Inventors:** Prabhakar Kondaji Jadhav,
Wilmington, Del.; Joseph James
Petratis, Glenmoore, Pa.; Douglas
Guy Batt, Wilmington, Del.

[73] **Assignee:** The DuPont Merck Pharmaceutical
Company, Wilmington, Del.

[21] **Appl. No.:** 770,538

[22] **Filed:** Dec. 20, 1996

Related U.S. Application Data

[60] **Provisional application Nos.** 60/009,088, Dec. 22, 1995, and
60/025,699, Aug. 9, 1996.

[51] **Int. Cl. ⁶** C07D 403/14; C07D 401/14;
A61K 31/54; A61K 31/535

[52] **U.S. Cl.** 514/211; 544/238; 544/262;
544/350; 544/67; 544/224; 544/333; 544/295;
544/337; 544/371; 544/361; 544/96; 544/98;
544/182; 544/179; 546/119; 546/244; 546/278.1;
546/268.1; 546/272.4; 548/361.1; 548/122;
548/127; 548/128; 548/131; 548/134; 548/136;
548/146; 548/254; 548/255; 548/262.2;
548/312.1; 540/545; 540/554; 540/575;
540/596; 540/597; 540/598; 540/599; 540/600;
540/601; 540/602; 540/603; 514/212; 514/228.2;
514/229.2; 514/227; 514/253; 514/256;
514/258; 514/242

[58] **Field of Search** 514/211, 212,
514/228.2, 229.2, 227, 253, 258, 256, 242;
540/596-603, 575, 554, 545; 548/361.1,
122, 128, 127, 131, 134, 136, 146, 254,
255, 262.2, 312.1; 544/238, 262, 350, 67,
224, 333, 295, 337, 371, 361, 96, 98, 179,
182

[56] **References Cited****U.S. PATENT DOCUMENTS**

4,808,405	2/1989	Smith et al.	424/94.3
4,950,764	8/1990	Nakamura et al.	248/243
5,187,157	2/1993	Kettner et al.	514/64
5,288,707	2/1994	Metternich	514/19
5,444,038	8/1995	James et al.	504/253

FOREIGN PATENT DOCUMENTS

0655439	5/1995	European Pat. Off.
9309795	5/1993	WIPO
9408962	4/1994	WIPO
9504531	2/1995	WIPO
9514683	6/1995	WIPO
9517397	6/1995	WIPO
9620192	7/1996	WIPO
9637492	11/1996	WIPO

Primary Examiner—Matthew V. Grumbling

Attorney, Agent, or Firm—Blair Q. Ferguson

[57] **ABSTRACT**

This invention relates to novel heterocycles including 3-[1-[3-(imidazolin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2-(benzyloxycarbonylamino)propionic acid, which are useful as antagonists of the $\alpha_v\beta_3$ integrin and related cell surface adhesive protein receptors, to pharmaceutical compositions containing such compounds, processes for preparing such compounds, and to methods of using these compounds, alone or in combination with other therapeutic agents, for the inhibition of cell adhesion, the treatment of angiogenic disorders, inflammation, bone degradation, cancer metastasis, diabetic retinopathy, thrombosis, restenosis, macular degeneration, and other conditions mediated by cell adhesion and/or cell migration and/or angiogenesis.

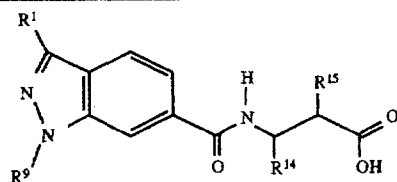
16 Claims, No Drawings

5.760.028

143

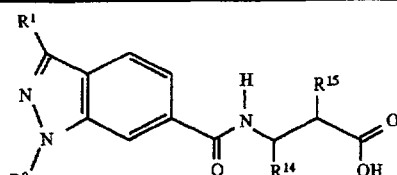
144

TABLE 3



Ex. No.	R ¹	R ⁹	R ¹⁴	R ¹⁵	MS
3001	imidazol-2-ylamino-(CH ₂) ₃	H	H	H	
3002	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHCOOCH ₂ Ph	
3002a	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHCOOCH ₂ Ph	
3002b	tetrahydropyrimidin-2-ylamino-(CH ₂) ₃	H	H	NHCO ₂ CH ₂ Ph	
3002c	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHCO ₂ CH ₂ Ph	
3003	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHCO ₂ CH ₂ C ₆ H ₄ -(2-CH ₃)	
3004	tetrahydropyrimidin-2-ylamino-(CH ₂) ₃	H	H	NHCO ₂ CH ₂ C ₆ H ₄ -(3-CH ₃)	
3005	benzimidazol-2-ylamino-(CH ₂) ₃	H	H	NHCO ₂ CH ₂ C ₆ H ₄ -(4-CH ₃)	
3006	2-aminopyridin-6-yl-(CH ₂) ₃	H	H	NHCO ₂ CH ₂ -(2-pyridinyl)	
3007	2-iminoazepin-7-yl-(CH ₂) ₃	H	H	NHCO ₂ CH ₂ -(3-pyridinyl)	
3010	imidazol-4-ylamino-(CH ₂) ₃	H	H	NHCO ₂ CH ₂ -(2-thiazolyl)	
3015	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHCO ₂ CH ₂ -(4-isoxazolyl)	
3016	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHCO ₂ CH ₂ -(2-thienyl)	
3017	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHCO ₂ n-Bu	
3018	tetrahydropyrimidin-2-ylamino-(CH ₂) ₃	H	H	NHCO ₂ i-Bu	
3019	benzimidazol-2-ylamino-(CH ₂) ₃	H	H	NHCO ₂ t-Bu	
3020	2-aminopyridin-6-yl-(CH ₂) ₃	H	H	NHSO ₂ Ph	
3020a	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ Ph	
3020b	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ Ph	
3020c	tetrahydropyrimidin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ Ph	
3020d	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ Ph	
3021	2-iminoazepin-7-yl-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₄ -(2-CH ₃)	
3021a	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₃ -(2,6-Me ₂)	
3021b	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,4,6-Me ₃)	
3021c	imidazol-1-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-Ph)	
3021d	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-Ph)	
3021e	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-Ph)	
3021f	tetrahydropyrimidin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-Ph)	
3021g	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(3-pyridyl))	
3021h	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(4-pyridyl))	
3021i	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(2-furyl))	
3021j	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(3-furyl))	
3021k	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(5-pyrazolyl))	
3021l	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,4,6-Me ₃)	
3021m	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(3-pyridyl))	
3021n	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(4-pyridyl))	
3021o	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(2-furyl))	
3021p	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(3-furyl))	
3021q	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(5-pyrazolyl))	
3021r	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,4,6-Me ₃)	
3021s	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(3-pyridyl))	
3021t	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(4-pyridyl))	
3021u	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(2-furyl))	
3021v	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(3-furyl))	
3021w	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Me ₂ -4-(5-pyrazolyl))	
3024	imidazol-4-ylamino-(CH ₂) ₃	H	H	NHSO ₂ -(2-pyridyl)	
3029	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ -(4-isoxazolyl)	
3030	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ -[4-(3,5-dimethyl)isoxazolyl]	
3030a	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ -[4-(3,5-dimethyl)isoxazolyl]	
3030b	tetrahydropyrimidin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ -[4-(3,5-dimethyl)isoxazolyl]	
3030c	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ -[4-(3,5-dimethyl)isoxazolyl]	
3031	imidazolin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₄ -(2-Br)	
3032	tetrahydropyrimidin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₄ -(3-Br)	
3033	benzimidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₄ -(4-Br)	
3034	2-aminopyridin-6-yl-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₄ -(2-F)	
3035	2-iminoazepin-7-yl-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₄ -(3-F)	
3038	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ -(1-naphthyl)	
3038a	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₃ -(2,6-Cl ₂)	
3038b	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ C ₆ H ₂ -(2,6-Cl ₂ -4-Ph)	
3043	imidazol-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ -i-Bu	
3044	pyridin-2-ylamino-(CH ₂) ₃	H	H	NHSO ₂ -t-Bu	
3045	imidazol-2-ylamino-(CH ₂) ₃	H	(3,4-methylenedioxy)phenyl		
3046	pyridin-2-ylamino-(CH ₂) ₃	H	(3,4-methylenedioxy)phenyl	H	
3047	imidazolin-2-ylamino-(CH ₂) ₃	H	(3,4-methylenedioxy)phenyl	H	
3048	tetrahydropyrimidin-2-ylamino-(CH ₂) ₃	H	(3,4-methylenedioxy)phenyl	H	
3049	benzimidazol-2-ylamino-(CH ₂) ₃	H	(3,4-methylenedioxy)phenyl	H	
3050	2-aminopyridin-6-yl-(CH ₂) ₃	H	(3,4-methylenedioxy)phenyl	H	

TABLE 3-continued

					
Ex. No.	R ¹	R ⁹	R ¹⁴	R ¹⁵	MS
3051	2-iminoazepin-7-yl-(CH ₂) ₃	H	(3,4-methylenedioxy)phenyl	H	
3054	imidazol-4-ylamino-(CH ₂) ₃	H	(3,4-methylenedioxy)phenyl	H	
3059	imidazol-2-ylamino-(CH ₂) ₃	H	3-pyridinyl	H	
3060	pyridin-2-ylamino-(CH ₂) ₃	H	3-pyridinyl	H	
3061	imidazolin-2-ylamino-(CH ₂) ₃	H	3-pyridinyl	H	
3062	tetrahydropyrimidin-2-ylamino-(CH ₂) ₃	H	3-pyridinyl	H	
3063	benzimidazol-2-ylamino-(CH ₂) ₃	H	3-pyridinyl	H	
3064	2-aminopyridin-6-yl-(CH ₂) ₃	H	3-pyridinyl	H	
3065	2-iminoazepin-7-yl-(CH ₂) ₃	H	3-pyridinyl	H	
3068	imidazol-4-ylamino-(CH ₂) ₃	H	3-pyridinyl	H	
3068a	imidazol-2-ylamino-CH ₂ (o-C ₆ H ₄)	H	H	NHSO ₂ -(1-naphthyl)	
3068b	imidazol-2-ylamino-CH ₂ (o-C ₆ H ₄)	H	H	NHCO ₂ CH ₂ Ph	
3068c	imidazol-2-ylamino-CH ₂ (o-C ₆ H ₄)	H	H	NHSO ₂ C ₆ H ₄ -(2,4,6-Me ₃)	
3068d	pyridin-2-ylamino-CH ₂ (o-C ₆ H ₄)	H	H	NHSO ₂ -(1-naphthyl)	
3068e	pyridin-2-ylamino-CH ₂ (o-C ₆ H ₄)	H	H	NHCO ₂ CH ₂ Ph	
3068f	pyridin-2-ylamino-CH ₂ (o-C ₆ H ₄)	H	H	NHSO ₂ C ₆ H ₄ -(2,4,6-Me ₃)	
3068g	imidazolin-2-ylamino-CH ₂ (o-C ₆ H ₄)	H	H	NHSO ₂ -(1-naphthyl)	
3068h	imidazolin-2-ylamino-CH ₂ (o-C ₆ H ₄)	H	H	NHCO ₂ CH ₂ Ph	
3068i	imidazolin-2-ylamino-CH ₂ (o-C ₆ H ₄)	H	H	NHSO ₂ C ₆ H ₄ -(2,4,6-Me ₃)	
3068j	imidazolin-2-ylamino-(m-C ₆ H ₄)	H	H	NHSO ₂ -(1-naphthyl)	
3068k	imidazolin-2-ylamino-(m-C ₆ H ₄)	H	H	NHCO ₂ CH ₂ Ph	
3068l	imidazolin-2-ylamino-(m-C ₆ H ₄)	H	H	NHSO ₂ C ₆ H ₄ -(2,4,6-Me ₃)	
3075	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCO ₂ CH ₂ Ph	
3076	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCO ₂ CH ₂ C ₆ H ₄ -(3-CH ₃)	
3077	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCO ₂ CH ₂ (3-pyridinyl)	
3078	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCO ₂ CH ₂ (2-thiazolyl)	
3079	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCO ₂ CH ₂ (2-thienyl)	
3080	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCO ₂ CH ₂ (5-isoxazolyl)	
3081	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCO ₂ n-Bu	
3082	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCO ₂ Ph	
3083	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCOCH ₂ Ph	
3084	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCOCH ₂ CH ₂ Ph	
3085	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCOCH=CHPh	
3086	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCOCH ₂ (3-pyridinyl)	
3087	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCOCH ₂ (2-thienyl)	
3088	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCOCH ₂ (cyclohexyl)	
3089	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCONn-Bu	
3090	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHCONHCH ₂ Ph	
3091	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ Ph	
3092	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₄ -(4-CH ₃)	
3093	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₃ -(2,6-CH ₃) ₂	554.4
3094	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₂ -(2,4,6-CH ₃) ₃	568.4
3095	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ (3-pyridyl)	
3096	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ (2-thienyl)	
3097	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ (2-thiazolyl)	
3098	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ [4-(3,5-dimethyl)isoxazolyl]	
3099	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₄ -(4-Br)	
3100	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₄ -(4-F)	
3101	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₃ -(2,6-Cl ₂)	594.3
3102	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ (2-naphthyl)	
3103	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ (1-naphthyl)	
3104	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₄ -(4-Ph)	
3104a	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₄ -(4-pyridyl)	
3104b	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₄ -(2-oxazolyl)	
3104c	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₄ -(3-pyrazolyl)	
3105	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₂ -(4-Ph-2,6-dimethyl)	630.3
3105a	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₂ -(4-(3-pyridyl)-2,6-dimethyl)	
3105b	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₂ -(4-(2-oxazolyl)-2,6-dimethyl)	
3105c	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₂ -(4-(3-pyrazolyl)-2,6-dimethyl)	
3105d	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₂ -(4-(4-pyridyl)-2,6-dimethyl)	
3105e	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₂ -(4-(2-furyl)-2,6-dimethyl)	
3105f	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₂ -(4-(3-furyl)-2,6-dimethyl)	
3106	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H ₂ -(4-Ph-2,6-dichloro)	670.3
3107	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ C ₆ H-(4-Ph-2,6-dimethyl-3-chloro)	
3108	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ CH ₂ Ph	
3109	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ n-Bu	
3110	imidazol-2-ylamino-(CH ₂) ₃	CH ₃	H	NHSO ₂ NHPh	

19

616



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 403/12, 401/14, A61K 31/505		A1	(11) International Publication Number: WO 97/03069
			(43) International Publication Date: 30 January 1997 (30.01.97)
(21) International Application Number: PCT/EP96/03026 (22) International Filing Date: 11 July 1996 (11.07.96) (30) Priority Data: 9514265.9 13 July 1995 (13.07.95) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): COCKERILL, George, Stuart [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). CARTER, Malcolm, Clive [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). McKEOWN, Stephen, Karl [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). VILE, Sadie [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). PAGE, Martin, John [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HUDSON, Alan, Thomas [GB/GB]; Long Lodge Cottage, Otford, Kent TN14 5RH (GB). BARRACLOUGH, Paul [GB/GB]; 27 Sevington Park, Loose, Near Maidstone, Kent ME15 9SB		(GB). FRANZMANN, Karl, Witold [GB/GB]; 6 Northstead Road, Tulse Hill, London SW2 3JW (GB). (74) Agents: REED, Michael, A. et al.; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: HETEROCYCLIC COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM			
(57) Abstract			
The invention is directed toward substituted heteroaromatic compounds which are protein tyrosine kinase inhibitors, in particular to substituted quinolines and quinazolines. Methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of psoriasis, fibrosis, atherosclerosis, restenosis, auto-immune disease, allergy, asthma, transplantation rejection, inflammation, thrombosis, nervous system diseases, and cancer.			

In an embodiment, the optional substituents for the carbocyclic or heterocyclic moiety, which may be present at any available position of said moiety, are selected from the group comprising:

$(\text{CH}_2)_q\text{S}(\text{O})_m\text{-C}_{1-4}\text{alkyl}$, $(\text{CH}_2)_q\text{S}(\text{O})_m\text{-C}_{3-6}\text{cycloalkyl}$, $(\text{CH}_2)_q\text{SO}_2\text{NR}^8\text{R}^9$,
 $(\text{CH}_2)_q\text{NR}^8\text{R}^9$, $(\text{CH}_2)_q\text{CO}_2\text{R}^8$, $(\text{CH}_2)_q\text{OR}^8$, $(\text{CH}_2)_q\text{CONR}^8\text{R}^9$, $(\text{CH}_2)_q\text{NR}^8\text{COR}^9$,
 $(\text{CH}_2)_q\text{COR}^8$, $(\text{CH}_2)_q\text{R}^8$, $\text{NR}^8\text{SO}_2\text{R}^9$ and $\text{S}(\text{O})_m\text{R}^8$,

wherein q is an integer from 0 to 4 inclusive; m is 0, 1 or 2;

R^8 and R^9 are independently selected from the group comprising hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, a 5- or 6-membered saturated or unsaturated heterocyclic ring which may be the same or different and which contains one or more heteroatoms which are selected from N, O or S, with the proviso that the heterocyclic ring does not contain two adjacent O or S atoms.

In a further embodiment the optional substituents for the carbocyclic or heterocyclic moiety are selected from the group comprising morpholine, piperazine, piperidine, pyrrolidine, tetrahydrofuran, dioxolane, oxathiolane and oxides thereof, dithiolane and oxides thereof, dioxane, pyridine, pyrimidine, pyrazine, pyridazine, furan, thiofuran, pyrrole, triazine, imidazole, triazole, tetrazole, pyrazole, oxazole, oxadiazole and thiadiazole.

Other optional substituents for the carbocyclic or heterocyclic moiety and also for other optionally substituted groups include, but are not limited to, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, nitro, amino, cyano, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkyl carbonyl, carboxylate and C_{1-4} alkoxy carboxyl.

Preferred compounds of the present invention include:

4-(1-benzyl-5-indolylamino)quinazoline;
 4-(1-benzyl-5-indolylamino)-6,7-dimethoxyquinazoline;
 4-(2-benzyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
 4-(2-benzyl-5-benzimidazolylamino)-quinazoline; ◀

4-(2-benzyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indazolylamino)-quinazoline;
4-(1-phenylsulphonyl-5-indolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-2,3-dihydroindolyl-5-amino)-6,7-dimethoxyquinazoline;
4-[3-(4-fluorophenyl)-6-indazolylamino]-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indolylamino)-6,7-diethoxyquinazoline;
4-[1-[2-(1,3-dioxolan-2-yl)-ethyl]-5-indazolylamino]-6,7-dimethoxyquinazoline;
4-(1-benzyl-6-indolylamino)-6,7-dimethoxyquinazoline;
4-(2-phenyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indolylamino)-6,7-methylenedioxyquinazoline;
4-(3-benzyl-5-benzimidazolylamino)-quinazoline;
4-(1-benzyl-5-benzimidazolylamino)-quinazoline;
4-(2-benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline;
4-(3-benzyl-5-benzotriazolylamino)-6,7-dimethoxyquinazoline;
4-(2-phenethyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-phenethyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(2-(2-pyridyl)-5-benzimidazolylamino)-quinazoline;
4-(2-benzylsulphonyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
and salts thereof, particularly pharmaceutically acceptable salts thereof.

Particularly preferred compounds of the present invention include:

4-(2-benzyl-5-benzimidazolylamino)-6,7-dimethoxyquinazoline;
4-(2-benzyl-5-indazolylamino)-6,7-dimethoxyquinazoline;
4-(1-benzyl-5-indazolylamino)-quinazoline;
4-(1-phenylsulphonyl-5-indolylamino)-6,7-dimethoxyquinazoline;
and salts thereof, particularly pharmaceutically acceptable salts thereof.

Certain compounds of the formula (I) contain asymmetric carbon atoms and are, therefore, capable of existing as optical isomers. The individual isomers and mixtures of these are included within the scope of the present invention. Likewise,